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PCT/GB 2005 / 0 0 1 1 0 6

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The Patent Office
Cardiff Road
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1. Your reference — MG/PMS/PB60815P

2. Patent application number *(The Patent Office will fill in his part)* — 0407025.6 — 29 MAR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Glaxo Group Limited
   Glaxo Wellcome House, Berkeley Avenue,
   Greenford, Middlesex UB6 0NN, Great Britain

   Patents ADP number *(if you know it)* 4735870003.

   If the applicant is a corporate body, give the country/state of its corporation. — United Kingdom

4. Title of the invention — Novel compounds

5. Name of your agent *(if you have one)*

   Corporate Intellectual Property

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   GlaxoSmithKline
   Corporate Intellectual Property (CN9 25.1)
   980 Great West Road
   BRENTFORD
   Middlesex TW8 9GS

   Patents ADP number *(if you know it)* 8072555006.

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — Yes

   Answer YES if:

   a) *any applicant named in part 3 is not an inventor, or*
   b) *there is an inventor who is not named as an applicant, or*
   c) *any named applicant is a corporate body*

   Otherwise answer NO See note (d)

Patents Form 1/77

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Continuation sheets of this form	0
Description	14
Claim(s)	2
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10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature(s) M Gibson

Date: 29-Mar-04

12. Name and daytime telephone number of person to contact in the United Kingdom — M Gibson 01279 644841

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a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505
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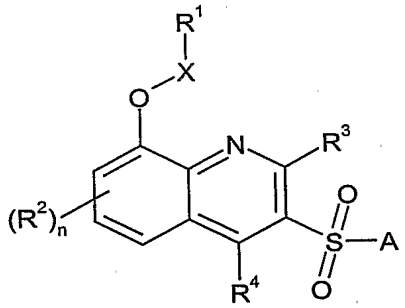
NOVEL COMPOUNDS

This invention relates to novel quinoline compounds having pharmacological activity, to processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

JP 02262627 (Japan Synthetic Rubber Co) describes a series of substituted quinoline derivatives useful as wavelength converting elements. WO 00/42026 (Novo Nordisk) describes a series of quinoline and quinoxaline compounds for use as GLP-1 agonists. WO 04/000828 (Biovitrum AB) describe a series of bicyclic sulfone or sulfonamide compounds which are claimed to be useful in the treatment or prophylaxis of a 5-HT_6 receptor related disorder. WO 00/71517 describes a series of phenoxypropylamine compounds as 5-HT_{1A} receptor antagonists which are claimed to be useful as anti-depressants.

A structurally novel class of compounds has now been found which also possess affinity for the 5-HT_6 receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents a group of formula $-NR^aR^b$ or a nitrogen containing heterocyclyl group optionally substituted by one or more (eg. 1 to 4) C_{1-6} alkyl groups;

X represents a bond, $-(CR^cR^d)-$, $-(CR^cR^d)-(CR^eR^f)-$, $-(CR^cR^d)-(CR^eR^f)-(CR^gR^h)-$, $-C_{3-8}$ cycloalkyl- or –heterocyclyl-, wherein said C_{3-8} cycloalkyl and heterocyclyl groups may be optionally substituted by one or more (eg. 1 to 4) C_{1-6} alkyl groups; such that when R^1 represents $-NR^aR^b$, X does not represent a bond;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h independently represent hydrogen or C_{1-6} alkyl;

R^2 represents halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

n represents 0 to 3;

R^3 and R^4 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
A represents an –aryl, -heteroaryl, -aryl-aryl, -aryl-heteroaryl, -heteroaryl-aryl or –heteroaryl-heteroaryl group;
wherein said aryl and heteroaryl groups of A may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or R^7 and R^8 together with the nitrogen atom to which they are attached may form a nitrogen containing heterocyclyl or heteroaryl group;
or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes single and fused rings for example, phenyl or naphthyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen fused to a benzene or monocyclic heteroaryl ring. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, diazepanyl, azepanyl, dihydroimidazolyl, tetrahydropyranyl, tetrahydrothiapyranyl and tetrahydrofuranyl. Suitable examples of benzofused heterocyclic rings include dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl, tetrahydrobenzazepinyl and tetrahydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

Preferably, R^1-X- represents $-(CH_2)_2-N(Me)_2$, $-CH_2$-(1-methyl-2-pyrrolidinyl), $-CH_2$-(2-pyrrolidinyl), $-(CH_2)_2-$(1-pyrrolidinyl), -3-pyrrolidinyl or $-C(H)(Me)-C(H)(Me)-N(Me)_2$.
Preferably, X represents a bond, $-CH_2-$, $-C(H_2)-C(H_2)-$ or $-C(H)(Me)-C(H)(Me)-$;
Preferably, R^a and R^b both represent C_{1-6} alkyl (eg. methyl).
Preferably, R^c and R^d either both represent hydrogen or one represents hydrogen and the other represents C_{1-6} alkyl (eg. methyl).
Preferably, R^e and R^f either both represent hydrogen or one represents hydrogen and the other represents C_{1-6} alkyl (eg. methyl).
Preferably, n represents zero.
Preferably, R^3 and R^4 both represent hydrogen.
Preferably, A represents –aryl (eg. phenyl) optionally substituted by one or more halogen (eg. chlorine) atoms or -heteroaryl (eg. pyridyl), more preferably A represents –aryl (eg. phenyl) optionally substituted by a halogen (eg. chlorine), most preferably unsubstituted phenyl.

Preferred compounds according to the invention include examples E1-E7 as shown below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or

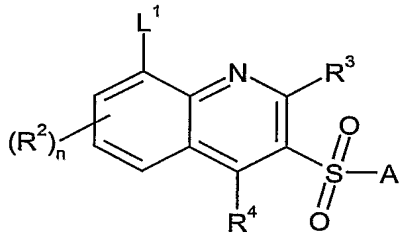
naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

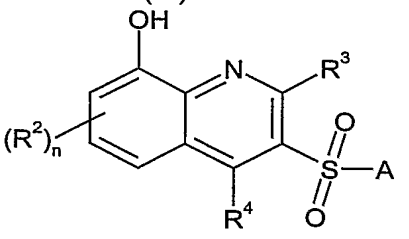
(a) reacting a compound of formula (II)



(II)

or an optionally protected derivative thereof, wherein R^2, R^3, R^4, n and A are as defined above and L^1 represents a leaving group such as a halogen atom or a trifluoromethylsulfonyloxy group;
with a compound of formula R^1-X-OH or an optionally protected derivative thereof, wherein R^1 and X are as defined above, and optionally thereafter removing any protecting groups; or

(b) reacting a compound of formula (III)



(III)

or an optionally protected derivative thereof; wherein R^2, R^3, R^4, n and A are as defined above;
with a compound of formula R^1-X-L^2 or an optionally protected derivative thereof, wherein R^1 and X are as defined above and L^2 represents a leaving group such as a halogen atom or a methylsulfonyloxy group, and thereafter optionally removing any protecting groups; or

(c) reacting a compound of formula (III) as defined above or an optionally protected derivative thereof, with a compound of formula R^1-X-OH as defined above or an optionally protected derivative thereof, and thereafter optionally removing any protecting groups;

(d) deprotecting a compound of formula (I) which is protected;

(e) interconversion to other compounds of formula (I) and/or forming a pharmaceutically acceptable salt and/or solvate.

Process (a) typically comprises the use of basic conditions and may be conveniently carried out using a compound of formula (II) where L^1 represents a fluorine atom and an alkali metal salt of a compound of formula R^1-X-OH in a suitable solvent such as *N,N*-dimethylformamide or dimethyl sulfoxide. The alkali metal salt of a compound of formula R^1-X-OH may be generated using a suitable alkali metal hydride such as sodium hydride. Alternatively, process (a) may be conveniently carried out using a compound of formula (II) where L^1 represents an iodine atom, in the presence of a base such as cesium carbonate and a suitable copper salt such as copper (I) iodide in a suitable solvent such as toluene. Process (a) may be optionally carried out at elevated temperature, e.g. 90 – 110 °C.

Process (b) typically comprises the use of basic conditions and may be conveniently carried out either (i) using an alkali metal salt of a compound of formula (III), generated using a suitable alkali metal hydride such as sodium hydride, in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran or (ii) using a base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide, acetone or 2-butanone. Process (b) may be optionally carried out at elevated temperature, e.g. reflux temperature or 90 – 110 °C.

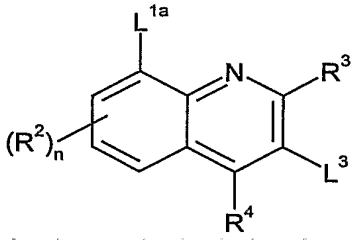
Process (c) typically comprises the use of Mitsonobu conditions, using a suitable substituted phosphine such as triphenylphosphine and an appropriate azodicarbonyl reagent such as diethyl diazodicarboxylate in a suitable solvent such as dichloromethane or tetrahydrofuran.

In processes (a), (b), (c) and (d) examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid. A further amine protecting group includes methyl which may be removed using standard methods for N-dealkylation (e.g. 1-chloroethyl chloroformate under basic conditions followed by treatment with methanol).

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, reductive alkylation, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, *N*-dealkylation of a compound of formula (I) wherein R^a represents an alkyl group to give a compound of formula (I) wherein R^a represents hydrogen. It will be appreciated that such interconversion may be interconversion of protected derivatives of formula (I) which may subsequently be deprotected following interconversion.

Compounds of formula (II) may be prepared as described in WO 03/080580.

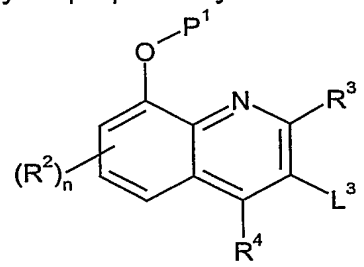
Compounds of formula (II) wherein L^1 represents a fluorine or chlorine atom may be prepared by reacting a compound of formula (IV)



(IV)

wherein L^{1a} is a fluorine or chlorine atom, L^3 is a suitable leaving group such as an iodine atom, and R^2, R^3, R^4, and n are as defined above; with a compound of formula A-SO_2-M, wherein A is as defined above and M is a metal residue such as sodium or potassium, in the presence of a copper (I) salt, e.g. copper (I) triflate or copper (I) iodide, in a suitable solvent such as dimethyl sulfoxide, anhydrous *N,N*-dimethylformamide or 1,4-dioxane, optionally including a ligand such as *N,N'*-dimethyl-ethylene-1,2-diamine and optionally in the presence of a base such as potassium carbonate.

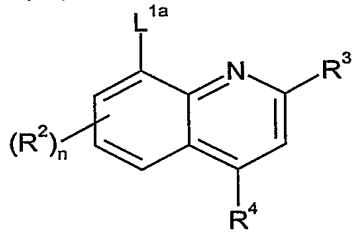
Compounds of formula (III) may be prepared by reaction of a compound of formula (V)



(V)

wherein L^3, R^2, R^3, R^4, and n are as defined above and P^1 represents a suitable protecting group such as a trialkylsilylethyl group (e.g. trimethylsilylethyl) or a trifluoromethylsulfonyloxy group, with a compound of formula A-SO_2-M as defined above in a manner similar to that used to prepare compounds of formula (II); and thereafter removing the protecting group, eg. when P^1 represents a trialkylsilylethyl group, such deprotection may typically be carried out using an alkali metal fluoride salt or a tetraalkylammonium fluoride salt (eg. tetrabutylammonium fluoride).

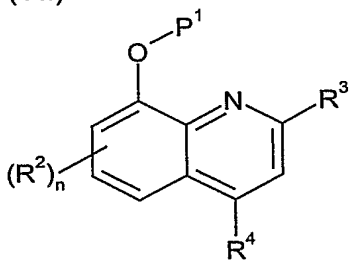
Compounds of formula (IV) wherein L^3 represents an iodine atom may be prepared by reacting a compound of formula (VI)



(VI)

wherein L^{1a}, R^2, R^3, R^4 and n are as defined above; with an iodinating agent such as *N*-iodosuccinimide in a suitable solvent such as acetic acid.

Compounds of formula (V) wherein L^3 represents an iodine atom may be prepared by reacting compounds of formula (VII)



(VII)

wherein R^2, R^3, R^4, n and P^1 are as defined above; with an iodinating agent such as *N*-iodosuccinimide in a suitable solvent such as acetic acid.

Compounds of formula (V) may also be prepared from compounds of formula (IV) as defined above by reaction with a compound of formula P^1-OH, wherein P^1 is as defined above, in the presence of a base such as sodium hydride in a suitable solvent such as tetrahydrofuran.

Compounds of formula (VI) and (VII) are either known in the literature or can be prepared by analogous methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT_6 receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline, mild cognitive impairment and vascular dementia), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia (in particular cognitive deficits of schizophrenia), stroke and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

5-HT_6 antagonists have the potential to be capable of increasing basal and learning-induced polysialylated neuron cell frequency in brain regions such as the rat medial temporal lobe and associated hippocampus, as described in WO 03/066056. Thus, according to a further aspect of the present invention, we provide a method of promoting neuronal growth within the central nervous system of a mammal which comprises the step of administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral

suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

8-Fluoro-3-iodoquinoline (D1)

N-Iodosuccinimide (8.1 g, 36.0 mmol, 2 eq.) was added to a solution of 8-fluoroquinoline (2.65 g, 18.0 mmol) in AcOH (13.25 ml, 5 vol). The mixture was stirred and placed in an oil bath which was then heated to 80°C. After 20 hrs 25min the flask was removed from the oil bath and allowed to cool to room temperature. CH_2Cl_2 (13.5 ml) was added, the solution was washed with 10% w/v $Na_2SO_{3\,(aq)}$ (23.5 ml), then with H_2O (13.5 ml) before being concentrated under reduced pressure. The crude product was pre-absorbed on silica and purified via column chromatography, eluting with 19:1 isohexane/EtOAc 1% Et_3N to yield 8-fluoro-3-iodoquinoline (D1) as a white solid (3.46 g, 12.7 mmol, 70%). ^1H NMR ($CDCl_3$, 400MHz) δ 7.40-7.45 (1H, m, Ar*H*), 7.50-7.52 (2H, m, Ar*H*), 8.58 (1H, t, *J* 1.7 Hz, Ar*H*), 9.09 (1H, d, *J* 2.0 Hz, Ar*H*).

Description 2

8-Fluoro-3-(phenylsulfonyl)quinoline (D2)

A flask was charged with copper (I) iodide (70 mg, 0.366 mmol, 0.1eq.), 8-fluoro-3-iodoquinoline (D1) (1.00 g, 3.66 mmol), phenylsulfinic acid sodium salt (1.56 g, 10.98

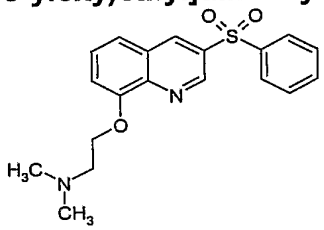
mmol, 3 eq.) and potassium carbonate (1.01 g, 7.32 mmol, 2eq). DMSO (5 ml) then *N, N'*-dimethylethylene-1,4-diamine (0.078ml, 0.2 eq.) was added, the mixture was stirred and placed in an oil bath which was heated to 90 °C.

After heating for 3 ½ hrs the flask was removed from the oil bath and allowed to cool to room temperature. The mixture was filtered and the cake was washed with DMSO (2 x 2 ml), the cake was then slurried with water (4 ml) and filtered, then washed with water (2 x 2 ml), sucked dry and further dried in at 50 °C under reduced pressure to yield 8-fluoro-3-(phenylsulfonyl)quinoline (D2) as an off-white solid (0.485 g, 46%).

^{1}H NMR ($CDCl_3$, 400MHz) δ 7.54-7.67 (5H, m, Ar*H*), 7.78 (1H, d, *J* 8.3 Hz, Ar*H*), 8.04 (2H, m, Ar*H*), 8.85 (1H, m, Ar*H*), 9.31 (1H, d, *J* 2.0 Hz, Ar*H*).

Example 1

[2-(3-Phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine (E1)

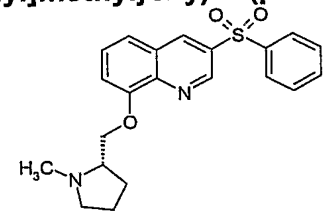


A round bottom flask was charged with copper (I) iodide (10 mg, 0.05 mmol), cesium carbonate (500 mg, 1.53 mmol), 2-dimethylaminoethanol (68 mg, 0.76 mmol) and 3-phenylsulfonyl-8-iodoquinoline (300 mg, 0.76 mmol) (WO 03/080580). The flask was then purged with argon and toluene (5 ml) introduced. The reaction mixture stirred was heated at reflux for 18 h. The reaction mixture was cooled and filtered. The filtrate was partitioned between dichloromethane (50 ml) and water (50 ml), the organic layer separated, dried over magnesium sulfate and concentrated to a brown paste. This was purified on silica, eluting with a dichloromethane/methanol (0 to 15%) gradient. [2-(3-phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine (E1) was obtained as a light brown solid (130 mg, 48%).

^{1}H NMR ($CDCl_3$) δ 2.40 (6H, s), 2.96 (2H, t, J = 6.0 Hz), 4.34 (2H, t, J = 6.2 Hz), 7.21-7.25 (2H, m), 7.51-7.56 (4H, m), 8.03 (2H, d, J = 7.1 Hz), 8.77 (1H, d, J = 2.0 Hz), 8.26 (1H, br s). MS: m/z $(M+H)^+$ 357, $C_{19}H_{20}N_2O_3S$ requires 356.

Example 2

8-({[(2*S*)-1-Methyl-2-pyrrolidinyl]methyl}oxy)-3-(phenylsulfonyl) quinoline (E2)



To a suspension of sodium hydride (60% dispersion in mineral oil) (50.4 mg, 1.26 mmol) in dry DMF (1.5 ml) in a pre-dried round bottomed flask was added [(2*S*)-1-methyl-2-

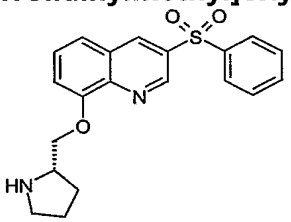
pyrrolidinyl]methanol (0.15 ml, 1.26 mmol) under an argon atmosphere. The resulting mixture was stirred at 40 °C for five minutes. A solution of 8-fluoro-3-(phenylsulfonyl)quinoline (D2) (200 mg, 0.7 mmol) in dry DMF (2 ml) was added in one portion and the resulting mixture was stirred at 60 °C under argon for 15 hours. The mixture was applied to an Isolute Flash SCX column (5 g sorbent), washed with methanol, then the compound eluted with dichloromethane – 10% methanolic ammonia (1:1). The residue was purified by flash chromatography (20 g silica gel) with a gradient of 10% methanolic ammonia in dichloromethane to give 8-({[(2*S*)-1-methyl-2-pyrrolidinyl]methyl}oxy)-3-(phenylsulfonyl)quinoline (E2) as a yellow solid

^{1}H NMR ($CDCl_3$) δ 9.27 (1H, d), 8.78 (1H, d), 8.00 (2H, dd), 7.55 (5H, m), 7.21 (1H, dd), 4.23 (1H, dd), 4.08 (1H, dd), 3.14 (1H, dt), 2.93 (1H, m), 2.54 (3H, s), 2.33 (1H, m), 2.15 (2H, m), 1.85 (2H, m).

Mass spectrum: $C_{21}H_{22}N_2O_3S$ requires 382; found 383 (MH^+)

Example 3

3-(Phenylsulfonyl)-8-{[(2*S*)-2-pyrrolidinylmethyl]oxy}quinoline hydrochloride (E3)



To a suspension of sodium hydride (60% dispersion in mineral oil) (36.4 mg, 0.91 mmol) in dry DMF (1.5 ml) in an oven dried round bottomed flask was added (2*S*)-2-pyrrolidinylmethanol (0.09 ml, 0.91 mmol) under argon atmosphere and the resulting mixture was stirred at 40 °C for five minutes. A solution of 8-fluoro-3-(phenylsulfonyl)quinoline (D2) (200 mg, 0.7 mmol) in dry DMF (2 ml) was added in one portion and the resulting mixture was stirred at 60 °C under argon over 15 hours. The mixture was applied to an Isolute Flash SCX column (5g sorbent) to washed with methanol then eluted with dichloromethane – 10% methanolic ammonia (1:1). the crude material was purified by flash chromatography (20 g silica gel) with a gradient of 10% methanolic ammonia in dichloromethane to afford 3-(phenylsulfonyl)-8-{[(2*S*)-2-pyrrolidinylmethyl]-oxy}quinoline.

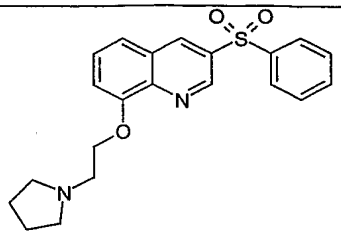
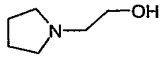
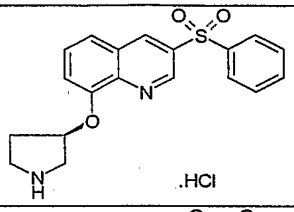
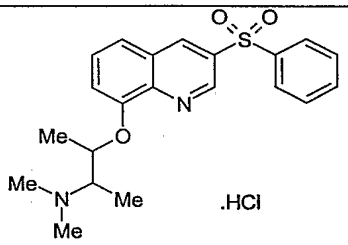
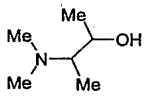
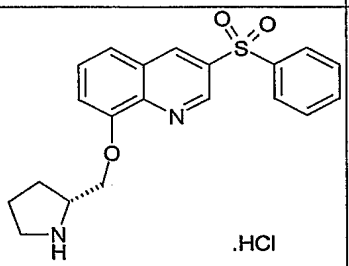
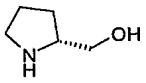
δ_H ($CDCl_3$): 9.26 (1H, d), 8.77 (1H, d), 8.02 (2H, dd), 7.54 (5H, m), 7.22 (1H, dd), 4.17 (1H, dd), 4.08 (1H, dd), 3.74 (1H, m), 3.01 (2H, m), 2.01 (1H, m), 1.86 (2H, m), 1.61 (1H, m).

This material was dissolved in methanol and transformed into the hydrochloride salt (E3) a yellow solid, by treating with HCl (0.1M in Et_2O, 0.7 ml) and stirring for 5 minutes followed by evaporation of the solvent.

Mass spectrum: $C_{20}H_{20}N_2O_3S$ requires 368; found 369 (MH^+)

Examples 4-7 (E4-E7)

Examples 4-7 were prepared in an analogous manner to the procedure described in either Example 1 or Example 3 from the corresponding hydroxyalkylamine indicated in the table below:

Example	Structure	Hydroxyalkylamine	Analogous Method to	Mass Spectrum
E4			E1	Requires 382; Found 383 (MH^+)
E5			E3	Requires 354; Found 355 (MH^+)
E6			E3	Requires 384; Found 385 (MH^+)
E7			E3	Requires 354; Found 355 (MH^+)

Pharmacological data

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following cyclase assay:

Cyclase Assay

0.5µl of test compound in 100% dimethylsulfoxide (DMSO) was added to a white, solid 384 well assay plate (for dose response measurements the top of the concentration range is 7.5µM final). 10µl of washed membranes of HeLa $5HT_6$ cells (for preparation see WO 98/27081) in basic buffer (50mM HEPES pH 7.4 (KOH), 10mM $MgCl_2$, 100mM

NaCl, 1μl/ml 3-isobutyl-1-methylxanthine (IBMX) (Sigma-Aldrich)) was added to all wells followed by 10μl 2 x ATP buffer (100μl/ml ATP and 1μl/ml 3-Isobutyl-1-methylxanthine (IBMX) (Sigma-Aldrich)) with 5-HT (at a concentration equivalent to a dose response of 4 x EC_{50}). The resultant mixture was then incubated at room temperature for 30-45 minutes to allow cAMP production.

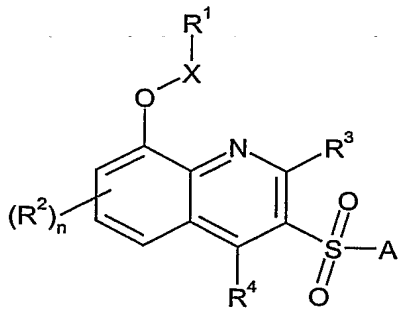
cAMP production was then measured using the DiscoveRx™ HitHunter™ chemiluminescence cAMP assay kit (DiscoveRx Corporation, 42501 Albrae Street, Fremont, CA 94538; Product Code: 90-0004L) or any other suitable cAMP measurement assay.

IC_{50} values were estimated from arbitrary designated unit (ADU) measurements from a Perkin Elmer Viewlux instrument using a four parameter logistic curve fit within EXCEL (Bowen, W.P. and Jerman, J.C. (1995), Nonlinear regression using spreadsheets. *Trends in Pharmacol. Sci.,* **16,** 413-417). K_i values were calculated using the method of Cheng, Y.C. and Prussof, W.H. (Biochemical Pharmacol (1973) **22** 3099-3108). pIC_{50} and pK_i are the negative log10 of the molar IC_{50} and K_i respectively.

The compounds of Examples E1- E7 were tested in the above cyclase assay and showed affinity for the 5-HT_6 receptor, having pKi values > 8.0 at human cloned 5-HT_6 receptors.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents a group of formula $-NR^aR^b$ or a nitrogen containing heterocyclyl group optionally substituted by one or more (eg. 1 to 4) C_{1-6} alkyl groups;

X represents a bond, $-(CR^cR^d)-$, $-(CR^cR^d)-(CR^eR^f)-$, $-(CR^cR^d)-(CR^eR^f)-(CR^gR^h)-$, $-C_{3-8}$ cycloalkyl- or –heterocyclyl-, wherein said C_{3-8} cycloalkyl and heterocyclyl groups may be optionally substituted by one or more (eg. 1 to 4) C_{1-6} alkyl groups; such that when R^1 represents $-NR^aR^b$, X does not represent a bond;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h independently represent hydrogen or C_{1-6} alkyl;

R^2 represents halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

n represents 0 to 3;

R^3 and R^4 independently represent hydrogen, halogen, cyano, $-CF_3$, $-CF_3O$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl or a group $-CONR^5R^6$;

R^5 and R^6 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

A represents an –aryl, -heteroaryl, -aryl-aryl, -aryl-heteroaryl, -heteroaryl-aryl or –heteroaryl-heteroaryl group;

wherein said aryl and heteroaryl groups of A may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^7R^8$ or $SO_2NR^7R^8$, wherein R^7 and R^8 independently represent hydrogen or C_{1-6} alkyl or R^7 and R^8 together with the

nitrogen atom to which they are attached may form a nitrogen containing heterocyclyl or heteroaryl group;
or solvates thereof.

2. A compound of formula (I) as defined in claim 1 which is:
[2-(3-Phenylsulfonylquinoline-8-yloxy)ethyl]dimethylamine;
8-({[(2*S*)-1-Methyl-2-pyrrolidinyl]methyl}oxy)-3-(phenylsulfonyl) quinoline;
3-(Phenylsulfonyl)-8-{[(2*S*)-2-pyrrolidinylmethyl]oxy}quinoline hydrochloride;
3-(Phenylsulfonyl)-8-{[2-(1-pyrrolidinyl)ethyl]oxy}quinoline;
3-(Phenylsulfonyl)-8-[(3*R*)-3-pyrrolidinyloxy]quinoline hydrochloride;
Dimethyl(1-methyl-2-{[3-(phenylsulfonyl)-8-quinolinyl]oxy} propyl)amine;
3-(Phenylsulfonyl)-8-{[(2*R*)-2-pyrrolidinylmethyl]oxy}quinoline hydrochloride;
or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition which comprises a compound as defined in claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.

4. A compound as defined in claim 1 or claim 2 for use in therapy.

5. A compound as defined in claim 1 or claim 2 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

6. The use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

7. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke.

8. A method of treating depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment, schizophrenia, cognitive deficits in schizophrenia and stroke which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof.